UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/826,680 | 04/16/2004 | Richard A. Weltzin | 06132/091001 | 1402 |

21559 7590 12/14/2007

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

| EXAMINER | |
|---|---|
| SNYDER, STUART | |
| ART UNIT | PAPER NUMBER |
| 1648 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 12/14/2007 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/826,680 | WELTZIN ET AL. | |
| | Examiner | Art Unit | |
| | Stuart W. Snyder | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7 and 10-24* is/are pending in the application.

4a) Of the above claim(s) *13* is/are withdrawn from consideration.

5)☒ Claim(s) *23 and 24* is/are allowed.

6)☒ Claim(s) *1-7, 10-12 and 14-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Claims*

1. Cancellation of pending original claims 8 and 9 and addition of new claims 14-24 in Applicants' filing of 9/24/2007 is acknowledged; amendment of claims 1-7 and 10-11 in the same filing is further acknowledged.

Claim 13 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/14/2007.

This application contains claim 13 drawn to an invention nonelected with traverse in the reply filed on 2/14/2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-7, 10-12, and 14-24 are pending and examined herein.

### *Claim Rejections - 35 USC § 112; 1st ¶*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-7 and 10-12 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the

time the application was filed, had possession of the claimed invention. The basis of the claims rejection as stated in the previous Office Action mailed 4/23/2007 is failure of Applicants to link sequence homology of claimed virus and SEQ ID NOs: 1 or 2 to the phenotype of claim 1 preamble, to wit, "attenuated" vaccinia virus. Previous claims 1-6 increasingly limit the degree of homology from "substantially identical" to "98% identical" to either SEQ ID No: 1 or 2. The specification characterizes certain functions of the claimed viruses and includes "plaque morphology, [virus] yield in MRC-5 cells, restriction endonuclease mapping patterns, the formation of cutaneous pocks in rabbits, mouse neurovirulence, and induction of protective immunity in mice". As stated in the previous Office Action, there is no teaching in the specification to correlate any of the desired phenotypic properties to specific regions of homology.

In addition to the Examiner's reasoning in the previous Office Action, a skilled artisan at the time of filing of the instant Application would not have known, *a priori*, from sequence or restriction digest data alone which derived virus isolates possess the desired phenotypic characteristics without performing phenotypic analysis because at the time of filing there was little teaching in the art regarding correlation of such phenotypic characteristics with sequence data. For example, Tartaglia, et al. (1992) and Kutinova, et al. (1995) both teach the common desire to obtain Dryvax-derived clones that retain the safety and immunogenicity profile of the parent strain or possess reduced virulence without sacrificing immunogenicity or growth characteristics required to prepare high titer,

pharmaceutically acceptable vaccines. However, neither correlates a particular region of the vaccinia genome with immunogenic or replicative properties. Similarly, prior to filing of the instant Application, most work correlating virulence, immunogenicity and sequence was limited to information at the gene scale. For example, Buller, et al. (1988) correlated vaccinia virus growth factor (VGF) with virulence by removing about half of each copy of the gene from the virus and observed reduced virulence; Šroller, et al. (1998) studied vaccinia virus virulence and immunogenicity in relationship to the presence or absence of a single gene (A44L).; Rosengard, et al. (2002) compared variola immune evasion (resulting in increased and persistent replication in the host) to that of vaccinia with respect to complement inactivation by one gene (SPICE vs. VGCP); Dunlop, et al. (2003) summarizes the earlier work of Stoller, et al. and Rosengard, et al. as well as speculates that others of approximately 80 genes located near the terminal regions of Orthopox viruses may be responsible for immune evasion and/or increased virulence; Kim, et al. (2004) studied the binding of vaccinia virulence factor E3L in relationship to its binding to different conformations of DNA as explanation for its virulence and potential therapeutic development using it as target. Post filing, others studied another vaccinia virulence factor (N1L; see, Abrahams, et al. (2005) and Cooray, et al. (2007)) in relationship to its anti-apoptotic activity and neurovirulence. Indeed, very recent studies comparing ACAM2000 with a neurovirulent clone of vaccinia also derived from polyclonal Dryvax—CL3—revealed 572 point mutations and 53 insertions/deletions of

various sizes although the mutations of gross differences in 4 genes correlated with increased virulence of CL3 relative to ACAM2000 (see Osborne, et al. 2007). Thus, even highly skilled virologists at the time of filing or today would not be able to predict which mutations, within the claimed limitation of 0.005 to 5% sequence identity variation and except in the limited cases of gene deletions, would confer differences in vaccinia virus immunogenicity and/or virulence.

In contrast to the situation described above, it is well known to virologists that certain point mutations can result in reduced or enhanced replicative ability and/or immunogenicity. For example, limited point mutations (1-4 amino acids; 4/10000 bases or ~0.01-0.04% difference in the genome) of HIV protease results in reduced enzymatic competence and thus reduced replicative capacity of the virus. However, such mutations may confer survival advantages to the virus if the context of viral replication includes certain protease-specific anti-viral therapeutics; in such case, mutant viruses would quickly out number wild-type virus--this phenomena is observed daily in humans naturally infected with HIV and undergoing protease-based antiretroviral treatment regimens. Also, limited point mutations of the influenza virus results in differences in replicative and virulence phenotypes of the virus (see, Fislová and Kostolanský, 2005; 4/13500 or 0.007-0.03% difference in genomes). Thus, although retroviruses and influenza viruses differ significantly from Orthopox viruses in replication strategies and genomic makeup, the relevant point is that small differences in one or two genes may confer large differences in infectivity of the host and

pathogenesis of the viruses. Transferring the teachings from the two examples to what is known about pox viruses, it is highly possible that one or more point mutations of the 1-4 identified Orthopox virulence factors would result in altered replication and/or virulence of the mutant viruses. Roughly estimating percent changes in genome identity reveals that theoretically a change in as little as 0.002-0.01% (or 4-16 out of 200,000 bases) might result in significant changes in virulence of the mutant viruses. Clearly this is a theoretical treatment of mutational analysis, but the underlying logic—point mutations in DNA sequence may result in altered virulence and/or immunogenic phenotypic viruses--easily transfers to Orthopox viruses. And, thus it is not the per cent deviation of genetic identity per se that is responsible for virus phenotype but the location and types of mutation of the virus. Quite simply, no one knew at the time of filing, where and how to mutate either ACAM1000 or ACAM2000 clones of vaccinia without increasing virulence or decreasing the immunogenicity of the resultant virus AND the specification didn't teach such information.

The Examiner has carefully considered Applicants' arguments and found them not persuasive. Applicants' attempt to overcome the rejection by more stringently limiting the difference in genetic variability of ACAM1000 or ACAM2000 progeny viruses. However, as seen above, it is not necessarily and/or merely the percent deviation of sequence identity that is significant in maintaining desired phenotypic characteristics of the virus, but the location and type of mutation that the virus can tolerate and maintain desired phenotypes. As shown above, small changes

in the virus genome may result in changes in host/virus populations under anti-viral therapeutic pressure—the same phenomena would occur if mutations conferred replicative advantage under immunologic pressure. Furthermore, the amended claim 7 is drawn to an "attenuated vaccinia virus comprising a nucleotide sequence...or SEQ ID NO:244". However, the reference sequence is a protein sequence and thus the claim makes no sense.

In view of the above arguments and those of record, Applicants' rebuttal arguments are not convincing. Therefore, rejection of claims 1-7 and 10-12 is **MAINTAINED** and applied to new claims 14-21.

***Claim Rejections - 35 USC § 112; 2nd ¶***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. The previous rejection of claims 1-7 and 10-12 under 35 USC § 112; 2nd ¶ is **WITHDRAWN** in view of Applicants' amendment of the claims.

5. Claims 7, 10-11, and 17-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 is drawn to a vaccinia virus "comprising a nucleotide sequence that is identical to a fragment of SEQ ID NO: 1" or 2 or the complement thereof; the recited limitation of the claim is that the [nucleotide] fragment has the sequence of SEQ ID NO:244. This limitation makes the claim nonsensical because SEQ ID NO:244 is a amino acid

sequence not a nucleotide sequence. As such, the claim is indefinite; claims 10-11 and 17-18 depend on claim 7 and are therefore indefinite also.

***Claim Rejections - 35 USC § 102/103***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-6 and 12 stand rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dumbell and Richardson. The claims, as amended, are drawn to a vaccinia virus clone defined by homology to ACAM1000 or ACAM2000. In the previous Office Action, the Examiner rejected the claims based on the similarity of the claimed viruses and buffalopox virus sequences.

Applicants' rebuttal arguments have been carefully considered but found to be unpersuasive. Applicants amended the claims to recite a narrow range of identity between the claimed virus and either ACAM1000 or ACAM2000; the recited range of identity is from 95% (claim 1) to 99.995% (claim 6). Analysis of the three

genes taught by the Singh, et al. reference (A27L, D8L, and H3L) reveals identity between ACAM2000 and buffalopox (BPV) virus of 100%, 99.1% and 99.5%. It is clear that there is a high degree of homology that occurs naturally between previously isolated BPV and Applicants' clones. Using the lowest of the three comparisons, Dumbell and Richardson clearly anticipate claims 1-3. Using a broad interpretation of claim 6 (>99.995% identity), it is also clear that, at least with respect to vaccinia A27L gene and the BPV homolog, that Dumbell and Richardson anticipates claims all of the claims 1-6.

Rejection of claims 1-6 and 12 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dumbell and Richardson is **MAINTAINED.**

7. Claims 19-21 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dumbell and Richardson. The claims are drawn to clonal strains of vaccinia having from 95-99.995% identical to SEQ ID NO:2 and pharmaceutical compositions thereof. As described above, Dumbell and Richardson clearly anticipate such clones for the simple reason that Applicants have not limited the necessary regions of identity between anticipatory virus isolates and the claimed clones; certainly in the region of A27L, there is strict identity between BPV and ACAM2000 as well as strict identity between the two virus isolates in the 5' regions of H3L and D8L genes.

***Double Patenting***

8. The terminal disclaimers filed on 9/24/2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of April 20, 2004 for US Patent No. 6,723,325 and October 3, 2026 for US Patent No. 7,115,270 have been reviewed and are accepted. The terminal disclaimers have been recorded.

9. Rejection of claims 1-7 and 10-12 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 9 of U.S. Patent No. 7115270 and claims 1 and 2 of U.S. Patent No. 6723325 is **WITHDRAWN** is view of approved Terminal Disclaimers filed 9/24/2007.

***Allowable Subject Matter***

10. Claims 22, 23 and 24 are allowed.

***Conclusion***

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart W. Snyder whose telephone number is (571) 272-9945. The examiner can normally be reached on 9:00 AM-5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stuart W Snyder
Examiner
Art Unit 1648

SWS

MARY E. MOSHER, PH.D.
PRIMARY EXAMINER